REMARKS

Applicants thank the Office for the attention accorded the present Application in the April 6, 2006, Office Action. In that Action, Claims 1-10 and 17-18 were rejected under 35 USC §103(a) as being unpatentable over Pearle, Carruthers et al., Abby et al., Oakley et al., and Behounek et al. in view of Rork et al.

The Office admits that the references Pearle, Carruthers et al., Abby et al., Oakley et al., and Behounek et al. do not expressly teach the incorporation of beta-blockers such as timolol, metoprolol, atenolol, and propranolol, and HMG-CoA reductase inhibitors such as pravastatin, folic acid, vitamin B6, and vitamin B12 into a single dosage unit.

The Office cites Rork et al. for the proposition that Rork et al. teaches a sustained release system that can include beta-blockers such as timolol, metoprolol, atenolol, and propranolol and statin cholesterol lowering agents such as simvastatin, pravastatin, and lovastatin. The Office then concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate beta-blockers such as timolol, metoprolol, atenolol, and propranolol with HMG-CoA reductase inhibitors such as pravastatin, folic acid, vitamin B6, and vitamin B12 into a single once-a-day dosage unit.

The Office relies on Rork et al. and the knowledge of one of ordinary skill in the art to establish a prima facie case of obviousness, and then responds to Applicants' previous arguments and prior numerous submissions of secondary evidence of

nonobviousness by stating that the arguments are not found persuasive.

The Office further continues to rely on In re Kerkhoven to state that evidence is required to overcome the prima facie obviousness rejection. Applicants respectfully traverse.

Applicants have amended independent Claims 1, 9, 10, 17, and 18 to limit the claims to a beta-blocker compliance dosage unit to enhance beta-blocker compliance in the treatment of cardiovascular disease.

Applicants remind the Office of the ***primary purposes*** of Applicants' invention is to increase compliance with taking medications, especially when multiple medications are required, as well as to simplify compliance. Applicants further state in Applicants' specification that patients with cardiovascular disease commonly take multiple medications and that the problems with achieving compliance include the inconvenience and confusion that arises especially for older patients with taking multiple medications. (See page 4, lines 16-21). Applicants' invention is provided to increase compliance among patients required to take a beta-blocker and a cholesterol-reducing agent. It is Applicants' proposed single dosage unit of a chlolesterol lowering medication and a beta-blocker that is one of the solutions to enhancing compliance with taking a beta-blocker, especially after a first myocardial event, that was not obvious at the time of Applicants' invention.

Applicants hereby incorporate their previous arguments and evidence as to the inapplicability of In re Kerkhoven. To recap the Office's counter arguments on the

applicability of In re Kerkhoven in view of Applicants' arguments on the differences in mechanisms of action, the Office listed several examples in the pharmaceutical art of two or more drugs having different mechanisms of action but concomitantly employed together. As Applicants have previously shown, the Office's rationale has no basis in logic. It is contrary to the Office's own obviousness analyses since, as shown by Applicants' arguments and evidence, the very same examples are all protected by patent, which presumably are nonobvious.

In addition, the Office's reliance on Rork et al. is misplaced. Rork et al. disclose a controlled-release delivery device. As Applicants have previously pointed out, Rork et al. disclosure only supports the controlled-release of a single, active, beneficial agent. No where in Rork et al. is there a suggestion to combine more than one active, beneficial agent. Applicants have asked the Office to cite the sections in the Rork disclosure that supports the Office's interpretation that the Rork disclosure teaches combining more than one beneficial agent. The Office has failed provide the citation(s) in Rork. The logical conclusion is that the Office cannot respond to such a request because the Rork disclosure does not contain any sections that support combining more than one beneficial agent in Rork's controlled-release deliver device. Thus, the Office has failed to make out a prima facie case of obviousness since the Office's contention of the teachings of Rork are unsupported.

Even though Applicants believe that the Office has failed to properly support its prima facie case of obviousness, Applicants have provided evidence of the recognition

of the problem, the need to solve the problem and the difficulties encountered in solving the problem. The classical indicia of nonobviousness is recognition of the need and the difficulties encountered by those skilled in the field. In re Dow Chemical Co., 847 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

Applicants' disclosure emphasizes that medication compliance is a problem. It further states that simplification is a desired goal to the inconvenience of taking multiple dosage units over a long period of time and to the confusion that arises especially for older patients with multiple medication regimens.

Applicants' previously submitted evidence Exhibit 1105-1, a study published May 1, 2005, among others, showed that long term adherence to statins and betablockers declined noticeably during the first two years. The study also reported that adherence was further negatively influenced if statin medications were prescribed after the initiation of beta-blockers. This report supports that compliance to multiple medications is influenced by the type of medication prescribed. Combining statins and beta-blockers in a single dose unit as claimed by Applicants would alleviate the negative influence associated with the type of medication prescribed.

Applicants' previously submitted evidence Exhibit 1105-2, which is a report published in November 2003 on interventions to improve patient adherence with medications for chronic cardiovascular disorders, states that there is consistent and robust evidence that simplifying medication dosage schedules leads to improved adherence. Applicants' combined dosage unit provides one means to simplify

medication dosage schedules. This report further confirms that adherence/compliance is a problem.

In yet another previously submitted reference Exhibit 1105-3, Applicants have shown that non-adherence or poor adherence to drug treatment is a significant problem in the management of chronic disease. This study concluded that beta-blocker use was lower in older patients, patients with airways disease, peripheral vascular disease, and heart failure but that these patients, unfortunately, were patients with the greatest potential to benefit from beta-blockers.

Applicants are submitting herewith Exhibit 0906-1, which is a copy of a study by Judith M. Kramer et al. entitled "National evaluation of adherence to beta-blocker therapy for 1 year after acute myocardial infarction in patients with commercial health insurance," American Heart Journal, Vol. 152, No. 3, September 2006, pages 454.e1-e8. The study reports that adherence to beta-blocker therapy (i.e. compliance with beta-blocker therapy) is only 45% at 1 year after hospital discharge for acute myocardial infarction.

The significance of this study is that all patients in the population study had prescription drug coverage so cost should not have limited adherence/compliance. As this study mentions, quality initiative programs by several national organizations including the American College of Cardiology Guidelines Applied in Practice, the American Heart Association's Get with the Guidelines, the Joint Commission on Accreditation of Health Care Organization's quality check, and the National Committee

for Quality Assurance's Health Plan Employer Data and Information Set have contributed to improvement in beta-blocker prescription rates within 7 days of discharge from 63% in 1996 to 93% by 2002. Yet, lack of compliance with beta-blocker therapy persists even though the prescription rates have increased.

The above-mentioned evidence is only a portion of the evidence submitted by Applicants to support their argument that there is a long felt need to solve the medication compliance problem. Medication compliance is a complicated problem. The studies have illustrated that the person of ordinary skill in the art has long recognized the problem but that the problem of medication compliance persists, especially with chronic disease such as cardiovascular disease. Studies performed after Applicants' reduction to practice further confirm Applicants' nonobvious insight that compliance can be improved by simplification of multiple medication treatment regimens. The studies are further evidence that those of ordinary skill in the art have pondered on possible solutions to the problem of medication compliance, but that not one of the solutions suggested Applicants' claimed invention.

Applicants have also submitted the declarations of Dr. Gurwitz and Dr. Dean as to the compliance problem and the nonobviousness of Applicants' solution.

It is Applicants contention that compliance can be improved by simplifying the therapy regimen as well as reducing the number of different, individually administered medications, which contribute to individual non-compliance to medication therapy. Yet, the full survival benefits of beta-blockers can best be realized with sustained, chronic

therapy as summarized by Kramer et al. (See Exhibit 0906-1). Applicants have early on recognized that the use of single dose medication therapy for beta-blockers and cholesterol lowering agents could improve medication compliance.

In addition, Applicants have provided evidence showing unexpected results. The evidence, which was Exhibit 1105-4, was a study published on May 7, 2005 to determine the effect of combinations of medications in the secondary prevention of all cause mortality in patients with ischaemic heart disease. The study was significant for disclosing what was already known on the topic and for what the study added. It was known that statins are associated with improved survival in patients with ischaemic heart disease but that direct evidence was lacking for the effects of combinations of drugs in cardiovascular disease.

The study included 13,029 patients who had a first diagnosis of ischaemic heart disease. 2,226 cases were matched to 9,064 controls. The study reported that the treatments associated with the smallest reduction in all cause mortality were beta-blockers alone with a 19% reduction and statins alone with a 47% reduction.

The study further reported that the drugs associated with the greatest reductions in odds for all cause mortality was the combination of statins, aspirin and beta-blockers with an 83% reduction. The study is also noteworthy for the reduction in odds for all cause mortality for the combination of statins and beta-blockers with a 54% reduction. (See Table 2, Adjusted Odds Ratio).

This study is significant for the reason that it provides evidence of unexpected

results showing that certain combinations of drugs on all cause mortality in patients with ischaemic heart disease provided increased benefits over those of each drug individually, which was heretofore unknown, while others did not. For example, statins alone provided a 47% reduction in odds for all cause mortality and beta-blockers alone provided a paltry 19% reduction. Yet, the combination of statins and beta-blockers provided a 54% reduction in odds for all cause mortality in patients with ischaemic heart disease. The reduction in odds for all cause mortality in patients with ischaemic heart disease is greater for Applicants' combination of statins and beta-blockers than for either medication alone.

Applicants' claimed single dosage unit is not only a simplification of multiple medication treatment regimens, which was nonobvious at the time of Applicants' invention and since confirmed as one solution to the adherence/compliance problem, but also provides unexpected results. The unexpected results are the greater reduction in odds for all cause mortality not achieved by either medication alone. Applicants' claimed invention garners the unexpected reduction in odds with the simplification of medication treatment regimens together in a single dosage unit. As attested to by the declarations of Dr. Gurwitz and Dr. Dean and the various reports submitted as evidence that the problem persists even today, none of the solutions proffered included treatment regimen simplification by using a multi-medication, single dosage unit as claimed by Applicants.

The so-called objective criteria must always be considered, Graham v. John

Deere Co., 383 U.S. 1, 17-18 (1966), and given whatever weight is warranted by the evidence presented. *See* Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1572 (Fed. Cir. 1996) (considering failure of others to find a solution to the problem); Transmatic, Inc. v. Gulton Indus., Inc., 53 F.3d 1270, 1275 (Fed. Cir. 1995) (considering failure of others to make the invention).

Conclusion

It is clear that, when Applicants' invention is viewed as a whole, the prior art contains no suggestion to combine Applicants' cardiovascular treatment medications into a single dosage unit to enhance medication compliance. Where Applicants' components are similar to those components shown and disclosed in the prior art, the law requires that the prior art also contain some teaching, suggestion or incentive for arriving at Applicants' claimed structure. The Office has failed to provide this showing. On the other hand, Applicants have provided evidence of the limitations in the prior art relied upon by the Office, the inapplicability of In re Kerkhoven, the noncompliance problems, the under-utilization of medications, and the unexpected reduction in odds for Applicants' combinations of cardiovascular medications for all cause mortality in patients with ischaemic heart disease, and confirmation that non-adherence or poor adherence to drug treatment is still a significant problem in the management of chronic diseases.

In light of the above arguments, Applicants respectfully submit that Claims 1-10

and 17-18 of the present application contain allowable subject matter and that the 35 USC §103(a) rejections have been successfully traversed.

Applicants believe that all of the pending claims should now be in condition for allowance. Early and favorable action is respectfully requested.

The Examiner is invited to telephone the undersigned, Applicant's attorney of record, to facilitate advancement of the present application.

Respectfully submitted,

Dated: 9/20/06

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I hereby certify that this correspondence is being electronically transmitted to the United States Patent and Trademark Office by way of EFS Web on September 20, 2006.

Robert R Deleault

Acute Ischemic Heart Disease

National evaluation of adherence to β-blocker therapy for 1 year after acute myocardial infarction in patients with commercial health insurance

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Background Quality measures of evidence-based medications post–myocardial infarction have focused on prescription at hospital discharge. Yet survival benefits of these medications are best realized with sustained therapy. We sought to examine long-term β-blocker adherence over the first year after myocardial infarction in patients with commercial health insurance and prescription drug benefits.

Methods This multicenter analysis examined health plan records from members of 11 health plans who had myocardial infarction in 2001, survived at least 1 year, and maintained insurance coverage (N = 17 035). The primary outcome measure was adherence to β-blockers (defined as prescription claims covering ≥75% of days) for 360 days post-discharge. We also examined associations with adherence—time from discharge, health plan product (commercial or Medicare + Choice [M + C]), age (35-64 or ≥65), sex, and region.

Results For 360 days after discharge, only 45% of patients were adherent to β-blockers, with the biggest drop in adherence between 30 and 90 days. In a multivariable model, statistically significant predictors of lower adherence were participation in M + C product, residence in the Southeast, and age (driven by young participants in M + C and young females in commercial products).

Conclusions In a population of patients with health insurance and prescription drug coverage, adherence to β-blocker therapy in the first year after myocardial infarction is poor, indicating that factors other than medication cost are important determinants of long-term adherence. Quality improvement initiatives focused on long-term adherence are needed to realize maximal benefit from medical therapy in post–myocardial infarction patients. (Am Heart J 2006;152:454.e1-454.e8.)

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Funding/Support: Participating health plans contributed personnel time for work groups (listed in Appendix B) and for collection and reporting of data. The Council for Affordable Quality Healthcare (CAQH) contracted with PricewaterhouseCoopers to aggregate de-identified data submitted by health plans and to provide feedback to the plans on the quality of data. The CAQH also provided an honorarium to Duke University for its investigators' time in analyzing and interpreting the aggregated data and preparing the manuscript.

Role of the Sponsor: CAQH provided a project manager to support the CAQH Cardiac and Measurement Work Groups. Final decisions on study design and technical specifications were made by the CAQH Cardiac and Measurement Work Groups. The CAQH allowed Duke investigators full independence in the analysis and interpretation of the data. The manuscript was prepared by Duke investigators. Contributing authors provided review and approval.

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Approximately 7.2 million American adults have a history of myocardial infarction.[1] We have known since the mid-1980s that β-adrenergic blocking medications (β-blockers) administered long-term after myocardial infarction improve survival and reduce the risk of reinfarction. In a 1985 meta-analysis of randomized trials, Yusuf et al[2] estimated that the benefit of administering β-blockers long-term after myocardial infarction (1-4 years of follow-up) would confer a 23% relative improvement in survival and a 26% relative decrease in nonfatal reinfarction. These conclusions have since been corroborated in updated meta-analyses[3,4] by a recent randomized trial of post-infarction patients with left ventricular dysfunction in the thrombolytic/interventional era[5] and in observational trials using large databases.[6]

Multiple studies have demonstrated that despite these convincing data, β-blockers have been underprescribed at discharge after myocardial infarction.[7,8] Recently, several national organizations have instituted quality initiatives to increase prescribing of evidence-based

medications at discharge after myocardial infarction. These include the American College of Cardiology (ACC)'s Guidelines Applied in Practice (GAP), the American Heart Association (AHA)'s Get with the Guidelines, the Joint Commission on Accreditation of Health Care Organizations (JCAHO)'s quality check, and the National Committee for Quality Assurance (NCQA)'s Health Plan Employer Data and Information Set (HEDIS).[9-12] These programs currently report improved rates of β-blocker prescription at hospital discharge. The NCQA's HEDIS measure of β-blocker prescription within 7 days of discharge improved from 63% in 1996 to 93% by 2002.[12]

There has been considerably less study of long-term outpatient use of β-blockers in post-infarction patients.[6,13-15] Yet the full survival benefits of β-blockers can best be realized with sustained, chronic therapy.[2,3,5,16]

While poor adherence to medications is likely multifactorial, common concerns are the cost of medications and the availability of prescription benefits.[17,18] Therefore, we examined long-term medication adherence in a national sample of post–myocardial infarction patients with prescription drug coverage. Our goal was to describe long-term, post–myocardial infarction use of β-blockers, temporal trends in adherence, and factors that may be associated with lower long-term adherence.

Methods

Data were contributed by 11 health plans (Appendix A) belonging to the Council for Affordable Quality Healthcare (CAQH), a national, not-for-profit organization of health plans and networks organized to promote collaborative initiatives to simplify administrative processes and improve quality of care. A work group of participating health plans developed common technical specifications for data collection. Under these specifications, each plan analyzed their individual patient data and submitted aggregated, de-identified data to the CAQH. The CAQH provided aggregated data to investigators at Duke University Medical Center for analysis. The Duke University Health System's Institutional Review Board granted exemption from review for this study.

Study sample

Patients were included in the study if they were ≥35 years old, were hospitalized for an acute myocardial infarction (ICD-9 codes 410.x1) in calendar year 2001, and had survived for at least 1 year after myocardial infarction. For patients with multiple myocardial infarction admissions, data were reported only for the first event in 2001. Patients were excluded if they were not continuously enrolled in their health plan for at least 1 year after the index event, or if they did not have prescription drug benefits. Patients were also excluded if either inpatient or outpatient records indicated the following contraindications to β-blocker therapy: a diagnosis of hypotension (ICD-9 code 458), bradycardia (ICD-9 code 427.81), or heart block greater than first degree (ICD-9 codes 426.0, 426.12, 426.13, 426.2-4, 426.51-4, and 426.7) that occurred either during the index hospitalization or during the 360 days after discharge.

Outcome measures

The primary outcome measure in this observational study was adherence to β-blocker for the 360 days after discharge for MI. Secondary outcome measures included adherence to β-blocker over 30, 90, 180, and 270 days after discharge and the association of adherence over 360 days with the following predictor variables: age group, sex, health plan product (commercial vs Medicare + Choice [M + C]), and geographic region (Northeast, Southeast, Midwest, and West). For analysis, all commercial health plan products (health maintenance organization [HMO], preferred provider organization [PPO], point of service [POS], and indemnity) were combined due to overlap in product structures and small numbers of patients in some products. Adherence during discrete intervals (0-30, 31-90, 91-180, 181-270, and 271-360 days after infarction) was also described to assess the timing of drops in adherence. Documentation of prescription at discharge was not available in this data set.

Pharmacy claims were evaluated from 90 days before discharge for the qualifying myocardial infarction (to capture preexisting prescriptions) to 360 days after discharge. Any β-blocker on the HEDIS list of β-blockers[19] was considered; changes in specific β-blocker medication and dosage were not tracked. Similar to methods used by other investigators,[20] "covered days" was defined as the actual number of calendar days covered by a purchased prescription of β-blocker medication within each specified time interval (ie, a 90-day supply dispensed on the 45th day had 46 days counted in the 0-90 day interval and 44 days in the 91-180 day interval). "Proportion of days covered (PDC)" was defined as the number of covered days of β-blocker divided by the number of calendar days in the measurement period. Patients were considered "adherent" if the PDC was ≥75%, a number similar to other studies of adherence in the literature.[14,20,21]

Data collection

Health plans aggregated data by type of health plan product (HMO, POS, PPO, indemnity plan or M + C) and by two age groups, 35 to 64 and ≥65 years. They dichotomously reported the number and percentage of patients who were 0 to 74% versus 75% to 100% adherent, based on the proportion of covered days in the relevant period. Age was determined as of December 31, 2001. Health plans also provided mean age of patients in their plan by commercial and M + C products. For descriptive purposes only, the plans used claims data to provide the number and percentage of patients with the following comorbidities: chronic obstructive pulmonary disease, diabetes, heart failure, hypertension, hyperlipidemia, or renal disease.

Statistical methods

Because health plans provided only aggregate data, estimated mean age for the overall population and each health plan product was calculated as a weighted average of the mean age from each health plan. Other population characteristics were summarized by frequencies and percentages. The proportion of patients adherent by health plan product (commercial vs M + C) was summarized separately for

Table I. Population characteristics

	Number and percentage of patients by age group		
	Total	**35-64 y**	**65+ y**
No. of patients	17035 (100)	12183 (71.5)	4852 (28.5)
Sex			
Male	12013 (70.5)	9329 (76.6)	2684 (55.3)
Female	5022 (29.5)	2854 (23.4)	2168 (44.7)
Age*, mean (SD)	60.2 (11.4)		
Region			
Northeast	8876 (52.1)	5649 (46.4)	3227 (66.5)
Midwest	3828 (22.5)	3336 (27.4)	492 (10.1)
West	2229 (13.1)	1512 (12.4)	717 (14.8)
Southeast	2102 (12.3)	1686 (13.8)	416 (8.6)
Type of health plan product			
Commercial	13616 (79.9)	11767 (96.6)	1849 (38.1)
HMO	4822 (28.3)	4338 (35.6)	484 (10.0)
PPO	4601 (27.0)	4039 (33.2)	562 (11.6)
POS	2714 (15.9)	2421 (19.9)	293 (6.0)
Indemnity	1479 (8.7)	969 (8.0)	510 (10.5)
M + C	3419 (20.1)	416 (3.4)	3003 (61.9)
Comorbidities† (n=13235)			
Lipid disorder	8604 (65.0)		
Hypertension	8088 (61.1)		
Heart failure	4780 (36.1)		
Diabetes	4151 (31.4)		
COPD	3684 (27.8)		
Renal disease	787 (5.9)		

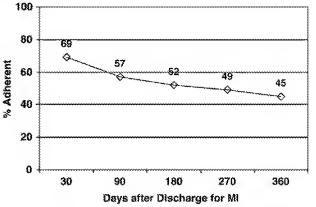
COPD, Chronic obstructive pulmonary disease.
*Age available for 99% (16890/17035) of population.
†Aggregate comorbidities available for 78% (13235/17035) of population.
Comparisons of product, sex, and region between age groups were statistically significantly different ($P < .001$).

patients aged ≥65 years and 35 to 64 years. Comparisons between groups were evaluated using χ^2 tests. Adherence over 360 days by region was described for all patients and separately for patients in commercial and M + C products. We used a multivariable logistic regression model to analyze the association of the predictor variables (age group, sex, region, and product) with 360-day adherence. Comorbidities were not included in the model because individual patient data were not available.

Results

Between January and December 2001, a total of 17035 patients covered by 11 health plans and prescription drug programs had myocardial infarction and subsequently survived for at least 1 year after discharge. These patients represented 48 states and the District of Columbia. Population characteristics are shown in Table I. The proportion of women among patients ≥65 years was considerably larger than in patients aged 35 to 64 years (44.7 vs 23.4%, respectively, $P < .0001$). In the overall population, mean age was 60.2 years (SD 11.4) with a range of 35 to

Figure 1



National adherence by cumulative time intervals.

100 years. The mean age for patients in commercial products was 56.3 years (SD 8.8), and the mean age for M + C was 75.0 years (SD 7.9).

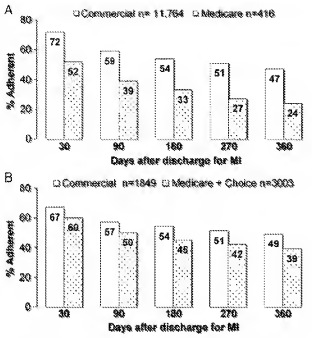
The largest number of patients was from the Northeast, followed by the Midwest. Approximately 20% of the population had M + C; 80% had commercial health plan products (28% HMO, 27% PPO, 16% POS, 9% indemnity). For patients aged 35 to 64 years, only 3.4% had M + C; for patients ≥65 years, 61.9% had M + C.

Population comorbidities indicate considerable disease burden (Table I). Almost two thirds of patients had a lipid disorder or hypertension. Nearly one third had diabetes; 36% had a diagnosis of heart failure.

Figure 1 shows adherence over the 360 days after discharge. In the period from discharge to 30 days after infarction, only 69% of patients were adherent to β-blocker medication. This proportion of adherent patients decreased progressively over longer cumulative periods. Over the full year after infarction, only 45% of patients were adherent.

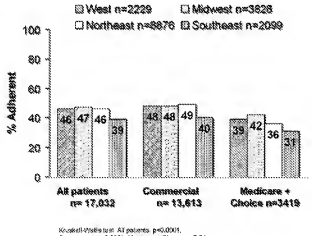
Data on national adherence for discrete time intervals (not shown) demonstrated that the greatest falloff in medication adherence occurs early, with a 15% absolute drop between the 0-30 day and 31-90 day periods (69%-54%, $P < .0001$). In both age groups and for every period, the proportion of patients adherent is considerably lower for patients in M + C products than in commercial products (Figure 2, *A* and *B*). In patients aged 35 to 64 years, only 24% of patients in M + C products were adherent to β-blockers over 360 days versus 47% of patients in commercial products ($P < .0001$). In patients aged ≥65 years, 39% of patients in M + C products and 49% of patients in commercial products were adherent over 360 days ($P < .0001$).

Figure 2



National adherence for cumulative time intervals by health plan product for patients aged 35 to 64 (**A**) and ≥65 years (**B**).

Figure 3



Adherence over 360 days by region and product. Kruskall-Wallis test: All patients: $P < .0001$; Medicare + Choice: $P = .04$.

Figure 3 shows adherence over 360 days by geographic region for the total population and separately by health plan product (commercial vs M + C). Overall and for both commercial and M + C products, adherence over 360 days was poorest in the Southeast.

Table II. Logistic regression results: factors associated with 360-day adherence

Main effects	Wald χ^2 statistic	P
Product	67.5	<.0001
Region (3 *df*)	52.5	<.0001
Age Group	18.7	<.0001
Sex	0.1	.78
Interactions		
Age group*sex	0.2	.66
Age group*product	8.3	.004
Sex*product	0.1	.78
Age group*sex*product	1.2	.28

Contrasts of interest	Odds ratio	95% CIs for odds ratio	P
Region: Southeast vs Northeast*	0.70	0.63-0.77	<.0001
Region: West vs Northeast*	0.97	0.88-1.07	.52
Region: Midwest vs Northeast*	0.98	0.91-1.06	.61
F vs M* within M + C age 35-64	1.11	0.58-2.14	.75
F vs M* within commercial age 35-64	0.87	0.80-0.95	.002
F vs M* within M + C age 65+	0.99	0.86-1.15	.92
F vs M* within commercial age 65+	1.15	0.95-1.38	.16
Age 65+ vs 35-64* within M + C males	2.02	1.56-2.63	<.0001
Age 65+ vs 35-64* within M + C females	1.80	0.97-3.34	.07
Age 65+ vs 35-64* within commercial males	0.99	0.88-1.12	.91
Age 65+ vs 35-64* within commercial females	1.31	1.11-1.54	.002

Model included region and 3-way interactions of age group, sex, and product. C index = 0.56.
*Indicates reference category.

Table II lists in order of importance (decreasing χ^2) the factors determined by logistic regression analysis to be associated with 360-day adherence. Product, region, and age group were statistically significant predictors of adherence over 360 days. The impact of product and region in the model confirms the descriptive results shown in Figures 2, *A* and *B*, and 3.

Overall, age is predictive in the logistic regression model. As can be seen by the Contrast test results (Table II), this is driven both by lower adherence in the younger (35-64 years) M + C participants, a unique subgroup of disabled patients and those with end-stage renal disease, and by lower adherence in younger women within commercial products.

Although the results did not show an overall effect of sex, the subgroup of women aged 35 to 64 years with commercial insurance products were less likely than men in their age group (female vs male OR = 0.87, $P = .002$) and less likely than older women (OR = 0.76, $P = .002$ for younger vs older women within

commercial) to adhere to β-blockers. This sex trend was reversed for the ≥65-year-old commercial participants (women vs men OR = 1.15, P = NS).

Discussion

This large, national sample of patients with commercial health insurance and prescription drug coverage definitively shows poor long-term outpatient adherence to β-blockers during the first year after myocardial infarction. Our study is among the first to examine long-term adherence to preventive therapy after myocardial infarction in a predominantly young, working-age population with pharmaceutical benefits.

Several studies in the elderly/retired population have shown poor long-term adherence to β-blockers after myocardial infarction.[6,13,14] Between 1987 and 1990, Soumerai et al[6] found that only 21% of elderly, low-income patients without contraindications to β-blockers had one or more prescription claims for β-blocker in the 90 days after discharge. Between 1994 and 1995, in a population of Medicare patients eligible for Medicaid benefits, Butler et al[13] found that 39% of patients discharged on β-blocker after myocardial infarction were no longer taking the drug at 1 year. In a later data set (1996-1998) of elderly patients in Quebec discharged on β-blocker after myocardial infarction, 26% of patients had not filled a prescription for β-blocker within 2 months of their 1-year anniversary after discharge.[14] Using an international registry of clinical trial sites (1999-2003), Eagle et al[15] found among the 65% of patients with follow-up 6 months after discharge that 12% had discontinued β-blocker medication. Long-term data for another evidence-based medication indicated post-infarction, HMG-coA reductase inhibitors (statins), also show poor long-term adherence. Jackevicius et al[22] found 2-year adherence rates to statins after acute coronary syndrome of only 40%.

Because all patients in this population had prescription drug coverage, cost should not have limited adherence. Still, we found disturbingly low rates of long-term adherence. These results have implications to the new Medicare prescription drug benefit. A national payment plan alone likely will not remedy poor long-term adherence to drugs that reduce morbidity and mortality after myocardial infarction.

Factors that determine long-term adherence are more complex and inherently different from those that determine initial prescription at discharge after myocardial infarction.[23,24] Upon discharge, the patient enters into the system of chronic care, which across the nation is much less organized and standardized than hospital-based care.[25] In addition to targeting community physicians to maintain prescribing, interventions to improve adherence must target patients and their family members. These individuals have the primary influence over decisions to maintain prescribed therapy. Factors that influence these decisions include their level of understanding about the benefits and risks of prescribed therapy, the complexity and duration of their medication regimen, their health beliefs, adverse effects they may attribute to their medication, cost, and inconvenience.[24] Additional factors are presence and accuracy of communication between hospital caregivers and community physicians who care for the patients after discharge.[25] Given the complexities of long-term adherence, it is not surprising that McDonald's systematic review of studies of medication adherence showed little relationship to sociodemographic factors such as age, sex, race, intelligence, and education.[24] Although our results did not show an overall effect of sex, it is interesting that younger women in the commercial products were less adherent than men in the same age group and less adherent than older women within commercial products. This finding is particularly intriguing given the epidemiologic data showing that younger, but not older, women who survive a hospitalization for myocardial infarction have higher 2-year mortality than men.[26] Younger women may perceive that they are less prone to heart disease. For exactly this reason, the AHA has mounted a "Go Red for Women" campaign, and the National Heart, Lung, and Blood Institute has started a "Heart Truth Campaign," both designed to educate women about their significant risk of heart disease.[27,28]

Our data show that the falloff in adherence is early. This suggests that to maintain β-blocker therapy long-term, interventions must be mounted in the first month or two after myocardial infarction.

The lower adherence in the Southeast is consistent with the regional results at hospital discharge found in the Cooperative Cardiovascular Project.[7] Reasons for lower adherence in the Southeast need to be explored in further research to identify factors involved.

The low rates of adherence in the small number of Medicare patients aged 35 to 64 years reflect the behavior of a special population of patients eligible at that age for Medicare—those with end-stage renal disease or total disability. In the over-65 population, the lower adherence for patients with M + C products compared with commercial products could have several explanations. With few exceptions, the commercial health plan products among CAQH members do not have dollar caps on prescription drug coverage, whereas most of the M + C products have prescription caps or tiered co-pays for generic versus patented medications.[29] Data from 2003 also indicate that 60% of all M + C health plan products cover only generic drugs. While 74% of enrollees in plans with generic-only coverage have unlimited generic benefit, the remaining had an annual cap of $500 or less. Thus, patients in

such plans taking patented medications or with annual prescription costs of generic products exceeding $500 will have out-of-pocket expenditures.

Tseng et al[18] recently documented the impact of exceeding annual prescription caps on strategies used by M + C patients to lower prescription costs. In patients exceeding caps, they found a statistically significant increase in the proportion of patients who reported using less prescribed medication than did control patients who did not exceed caps. Although our findings of lower adherence in M + C beneficiaries are consistent with Tseng's results, another confounding factor could be at play. If a patient in M + C reaches a prescription cap or requires a patented medication, he may purchase the prescription out of pocket. The CAQH data cannot distinguish between medication not taken and medication purchased out-of-pocket where no claim is filed. An attempt to examine this issue in future research could provide useful information as we consider the effect of the Medicare prescription drug benefit with a gap in coverage once a beneficiary's total drug costs reach a $2250 annual cap.[18]

Limitations

An important caveat is that these results are based purely on aggregated administrative data. Because adherence was reported dichotomously as ≥75% versus <75% PDC, it is not possible to examine degree of adherence as a continuous variable. Because individual patient data are not available, it is also not possible to associate individual patients' adherence early after discharge with later clinical outcomes. The administrative data were not validated using chart reviews. Thus, the number/proportion of patients actually prescribed a β-blocker at discharge is not documented. National HEDIS 2001 statistics indicate that 92.5% of commercial and 92.9% of M + C patients were prescribed β-blockers within 7 days of discharge. Assuming the HEDIS prescription estimate is correct, 93% of patients in this study were likely prescribed a β-blocker at discharge in 2001. The fact that only 69% of patients were adherent to β-blocker in the first 30 days suggests that approximately 24% of patients may not have initially filled their discharge prescription.

These data cannot account for doctors' verbal instructions to patients to change β-blocker dose. Verbal instruction to cut the dose in half would result in an underestimation of adherence. Any dose changes incorporated into new written or verbal prescriptions would be captured by our methods.

Adherence calculations were not adjusted for days spent in a hospital during the follow-up year. There would have been significant complexity in obtaining and programming these data, and it was thought likely to have minimal impact on adherence over a 360-day period of follow-up.

Although administrative data are limited in the conclusions that can be drawn, the advantages of this data set include its size and the fact that the claims being analyzed are derived under actual practice conditions. These data represent the entire unselected population of patients with MI in 2001 who had insurance with these health plans. The adherence of these patients would be more representative of patients in actual practice than adherence observed in a selective clinical trial population or in a registry requiring patient consent.

Future initiatives

To reap the potential benefit of β-blockers after myocardial infarction, quality efforts must refocus on long-term outpatient care. Similar to inhospital quality programs, initiatives are needed to measure performance indicators. Pay-for-performance approaches that have been utilized in other quality efforts may be applicable for long-term β-blocker adherence as well.

The CAQH initiated a national education program, ***heartBBEAT for life***, in collaboration with the AHA, ACC, American Academy of Family Physicians, and American College of Physicians to improve long-term adherence to β-blocker after myocardial infarction.[30] This program focuses on raising awareness and educating physicians, their patients, and public about the importance of maintaining β-blocker therapies post-MI.

The CAQH also shared its preliminary results with the NCQA, an organization that accredits health plans and develops HEDIS measures. The NCQA initiated a new HEDIS 2005 measure of 6-month adherence to β-blocker after myocardial infarction using CAQH methodology. The collaboration of health plans within CAQH and their interactions with NCQA on this matter are examples of collective leadership recently recommended as an approach to improve clinical quality across organizations.[31] Previous quality measures for discharge prescription of β-blocker s (HEDIS, JCAHO, Get With the Guidelines, GAP) have been associated with marked improvements in rates of discharge prescriptions over the last 10 years. The new long-term HEDIS measure for β-blocker use after myocardial infarction will likely provide an incentive for health plans to promote long-term adherence.

For additional efforts to improve long-term adherence, the motivations of all parties (physicians, patients, health plans, pharmaceutical companies, pharmacists, and nurses) should be well aligned as we seek to improve the health and safety of patients through better long-term adherence to life-saving medications.

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Appendix A

Participating health plans

Aetna, Inc
Anthem Blue Cross and Blue Shield
Blue Cross Blue Shield of Georgia
Blue Cross Blue Shield of Michigan
Blue Cross of California
CIGNA Corporation
Empire Blue Cross Blue Shield
First Health Group Corp
Health Net, Inc
Highmark Blue Cross Blue Shield
Independence Blue Cross
Oxford Health Plans, Inc
WellPoint Health Networks, Inc

Appendix B

Members of the Cardiac and/or Measurement Work Groups by organization

Aetna, Inc

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AultCare

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Blue Cross Blue Shield of Missouri

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Highmark Blue Cross Blue Shield

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Horizon Blue Cross Blue Shield of New Jersey

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Independence Blue Cross

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Oxford Health Plans, Inc

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WellPoint Health Networks, Inc

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